

McCormick et al
U.S. Serial No. 09/522,900
Page 8 of 15

REMARKS/ARGUMENTS

In response to the Rejection mailed October 24, 2005, Applicants have amended claims 1-3, 54 and 55, present new claim 57 and the following remarks. Claims 1-4, 6-23, 29, 37-40 and 54-57 are pending. Claims 5, 24-28, 30-36 and 41-53 have been canceled.

Applicants appreciate the examiner noting certain objects and rejections are withdrawn.

Claims 1-4, 6-23, 29, 37-40 and 54-56 were rejected under 35 USC 112, second paragraph as indefinite in several recitations.

Claim 1 was considered indefinite by reciting "encoded at least in part". The examiner urges it is "unclear what encodes the rest of the polypeptide self antigen." This rejection is respectfully traversed.

While the previous language was clear, the claim has been amended to avoid the offending language. As for the examiner's question, the remainder of the polypeptide can be very diverse. In claims 13+ a portion of the rest of the polypeptide self-antigen includes the artificial linker sequence. Other portions may include other peptide sequences for a variety of other optional purposes such as: part of the constant regions of the light and heavy chains (especially if the boundaries of the variable portions are unclear), sequences for expression, proper folding, packaging or secretion from the cell, adjuvant, antigenic, immunostimulatory or side-effect ameliorating sequences, vector replicating sequences, etc.

Claim 23 was considered indefinite in the recitation "at least about". The examiner contends that there is no specific concentration range based on activity. This rejection is traversed.

The functional abilities of the vaccine define a range of polypeptide amount as well. The examiner should appreciate that the actual boundaries of functionality will vary somewhat as the sequence of the polypeptide self-antigen and the patient condition will vary from patient to patient. Nonetheless, claim 23 recites a minimal amount of polypeptide to be used as the vaccine, which is clear.

McCormick et al
U.S. Serial No. 09/522,900
Page 9 of 15

The examiner contends that Hawkins et al and Caspar et al are close prior art with concentrations of 12.5 and 50 micrograms. These references are not close prior art because they involve different proteins. Even if the amounts are considered identical, the critical polypeptide differs and therefore these references do not constitute close prior art. Therefore, the examiner's point is moot. According, there is nothing indefinite in the use of this term in the present context.

Claims 1+ were considered indefinite in the recitation "a nucleic acid encoding a peptide sequence overlapping a peptide sequence encoded by said nucleic acid inn the cells of said tumor". The amount of overlap is unclear. This language has been amended to indicate what portion(s) of the sequence(s) in the tumor cells are found in the claimed polypeptide. Accordingly, this rejection should be withdrawn.

Claims 1-4, 6-23, 29, 37-40 and 54 were rejected under 35 USC 112, first paragraph, as the specification does not enable the present claims. The examiner questions whether the present invention can prevent or cure lymphomas in patients. More specifically the examiner objects to the use of the term "vaccine" because it does not prevent all problems associated with a disease. This rejection is respectfully traversed.

The term "vaccine" refers to a composition that functions via the immune system and in this field is properly used to describe the claimed composition. The examiner's comments that the vaccine does not prevent cell transformation to tumor cells and other non-immune system events are irrelevant. The references cited by the Examiner, call their polypeptide compositions vaccines (e.g. see the titles of Caspar et al and Hakim et al). There is no guarantee that a vaccine can prevent or cure anything 100% of the time, as it is well known that many commercial vaccines have limited periods and degrees of effectiveness or require boosters. An outbreak of mumps in the United States this spring emphasizes the point. From previous published vaccines for non-Hodgkin's B-cell lymphomas, and the data demonstrating the compositions used in the invention induce an immune response, the use of the "vaccine" language is appropriate. Accordingly, the rejection should be withdrawn.

McCormick et al
U.S. Serial No. 09/522,900
Page 10 of 15

Claims 1+ were considered not commensurate in scope with the specification as the examiner contends that the entire VH and VL domains with all of the CDRs “in their proper order and in the context of framework sequences” are required to mimic the natural epitope. In support, the examiner cites Benvenuti et al for support that conformational pairs are needed. This rejection is respectfully traversed.

The data in the specification as well as data in the prior art of record demonstrates that appropriate immune responses can be generated without the entire heavy and light chain and without being in the “context of framework sequences”. The exemplified molecules contain only part of the tumor antigen surface immunoglobulin. The domains somewhat resembling part of the heavy and light chains are linked by a different type of linkage and to different ends of the heavy and light chain-like moieties. Applicant’s molecules actually function as claimed. Therefore, it is improper for the Examiner to contend that the entire sequences are needed and certainly not all of the framework sequences. It is also improper to conclude that the sequences forming the epitope are held together in the same context because applicant’s single chain molecule links the domains in a different manner from the naturally occurring tumor antigen.

While evidence suggests that the three-dimensional configuration of the peptide sequences is critical, the examiner has not been established that the entire variable regions are needed and certainly not the entire supporting framework sequences. Benvenuti et al teach that for at least one example, one chain alone is not an effective antigen. However, this is not what applicants claim. The concept is also demonstrated by applicants also as the claimed antigen has two domains linked together by a linker selected from a library of linkers. If only one domain were needed to form the epitope, all linkers would be equally effective. This was not the case. Applicants found that many linkers did not allow the correct conformation to allow both domains to form the antigen’s epitope. Therefore, as recognized by Benvenuti et al, the correct folding of the antigen at the epitope is important. This feature is already recited in claim 1, section C). If the examiner considers Benvenuti et al does not work because it does not have the epitope, claim 1, section D) recites that the antigen has enough of the sequences to constitute the epitope so that there is an immune response against the tumor antigen epitope.

McCormick et al
U.S. Serial No. 09/522,900
Page 11 of 15

The exact boundaries of the epitope(s) are likely to vary from tumor antigen to tumor antigen. While the Examiner contends that all six CDRs are required, this hypothesis is not proven. Furthermore, the CDRs themselves are poorly defined hypothetical regions, not physically distinct portions of the molecule. It is improper for the Examiner to require applicants to conform to his interpretation of a hypothesis when applicants have presented experimental data of success in mimicking the natural tumor cell idiotype.

Claims 54 and 56 were considered to have language not be supported by the specification, particularly the language "not fused or conjugated to another polypeptide". This language is an accurate description of the antigens actually made in the examples. This characteristic is an inherent property of the molecules made in the examples and therefore adding such language to a claim is not new matter any more than adding language adding other inherent properties such as solubility, molecular weight, etc. Furthermore, the present invention is contrasted to prior art wherein an antigen is fused or conjugated to another polypeptide; therefore it is explicitly implied to be different from that prior art.

The examiner concludes the rejection stating "The disclosure...would not have led the skilled artisan to the presently claimed polypeptide, not conjugated or fused to another polypeptide." This conclusion is contradicted by fact. If the skilled artisan followed the specification examples exactly, the final product would be within "the presently claimed polypeptide, not conjugated or fused to another polypeptide." Accordingly, the rejection should be withdrawn.

Claims 1-4, 6-13, 17-23, 29 and 38 were rejected under 35 USC 102(b) as being anticipated by Caspar et al. The examiner contends that the fusion protein vaccine taught is the same as that claimed. The examiner contends the phrase "capable of" is not a positive limitation. This rejection is respectfully traversed.

Claim 1 has been amended to require the claimed polypeptide to do rather than being capable of doing. Claim 1 has been amended to avoid the word "includes" for the same reason.

McCormick et al
U.S. Serial No. 09/522,900
Page 12 of 15

Caspar et al uses a fusion protein of the tumor antigen sequences fused to GM-CSF. There is no indication that the epitope portion of the polypeptide sequence alone is capable for inducing an effective immune response. Furthermore, claims 2 and 3 were included in this rejection yet Caspar et al produces their polypeptide in insect cells rather than in plant cells. There is no indication that scFv molecule or the Caspar et al fusion molecule would be correctly folded when expressed in plants. As is known from applicants' experiments, a well-chosen linker is necessary to produce a functional protein. Caspar uses only one linker, (Gly3Ser)₄ which is frequently unacceptable. Accordingly, this rejection should be withdrawn.

Claims 1-4, 6-12, 17-23, 29 and 37-38 were rejected under 35 USC 102(b) as being anticipated by Hawkins et al. The examiner contends that Hawkins teaches an scFv mimicing the surface immunoglobulins of a B-cell lymphoma used as a vaccine. This rejection is respectfully traversed.

Hawkins et al teach immunizing with a nucleic acid. There is no showing that immunization with a polypeptide functions elicits the claimed immune response. Likewise, there is no suggestion that Hawkins et al can make a polypeptide that is obtainable from a cell correctly folded without renaturation. These features are recited in claim 1, sections C) and D). While one may dream such a thing is possible, the world of vaccines is full of failed attempts and unpredictability. Without a showing of a polypeptide with the claimed features, Hawkins et al does not anticipate the claims.

The examiner's comments regarding the language "capable of" are the same as in the rejection over Caspar et al. The same amendments and arguments apply for this rejection as well. Accordingly, the rejection should be withdrawn.

Claims 1-4, 6-23, 29, 37-40 and 54 were rejected under 35 USC 103 as being unpatentable over Caspar et al in view of Fiedler et al, Tang et al and Hakim et al. Caspar et al was applied above. The basis for the rejection is basically the same as previously. This rejection is respectfully traversed.

The examiner contends, "In response to these arguments, applicant has not pointed to any feature or features that are not taught or suggested by the combination of

McCormick et al
U.S. Serial No. 09/522,900
Page 13 of 15

references cited by the examiner." Briefly repeating some of the features mentioned before (should they not be considered "pointed to"):

1) None of the references disclose a purified polypeptide with the epitope that elicits an immune response against the tumor antigen epitope without an adjuvant. Fiedler et al and Tang et al do not involve vaccines but were applied to show different features. The rejection assumes that Casper et al and Hakim et al teach the corresponding polypeptide vaccine, but they do not. The single polypeptide protein vaccine in Caspar et al is fused to an adjuvant mouse GM-CSF. In Hakim et al, (an earlier paper from the same group of scientists), three different single chain peptides were attempted as vaccines. One was fused to mouse GM-CSF, one fused to IL-1B peptide and one was the scFv alone. While the scFv alone vaccine appears similar to the presently claimed invention, this vaccine did NOT elicit an immune response. See Table II where total IgG specific to scFv was 0 mg/ml. Also, Figure 5 shows that mice immunized with the scFv alone died at the same rate as control mice when challenged with the corresponding tumor cells.

In view of their published failure, and a need to use other vaccination techniques, the references teach that the present invention is not possible and teach away from its use. Therefore, none of the references disclose that it is even possible to produce the polypeptide vaccine, which is effective without an adjuvant.

2) None of the references indicate it possible to prepare an effective polypeptide antigen from a plant cell (claims 2-4). Fiedler et al produce a polypeptide in plants, which binds to another molecule in a fashion similar to an antibody. However, binding ability is different from the ability to elicit an effective immune response by interacting with all of the appropriate cells of the immune system. One can start with a library of random sequence polypeptides and some will bind to any given binding partner. However, that does not mean the same molecule(s) will make an effective immunogen for eliciting the appropriate immune response. The standards and exactness of the folding are higher for eliciting an appropriate immune response.

3) None of the references suggest a composition containing both an epitope vaccine polypeptide and other plant proteins, much less secreted proteins. Note claim 55 and new claim 57.

McCormick et al
U.S. Serial No. 09/522,900
Page 14 of 15

4) In a similar way, none of the reference suggests using a randomized linker for a two-domain polypeptide antigen. The Tang et al reference attempts many linkers between domains for a single chain antibody to obtain binding ability. Again binding ability is much easier to obtain than mimicking an epitope for eliciting an immune response. Further, in Tang et al these molecules are found in multiple copies on the surface of a bacteriophage, which allows for even less stringent binding ability than in Fiedler et al.

5) The randomized linkers in Tang et al are outside the claimed properties of the linkers claimed in dependent claims. Tang et al's linkers do not facilitates secretion (recited in claim 13 and 57), as their product is never secreted.

6) The randomized linkers in Tang et al are completely random whereas the present claims 14, 15 and 16 recite particular limits to the randomization process and require sequences for the linker, which are not found in Tang et al.

7) Claim 19 requires a "protective" immune response whereas the scFv used in the prior art of record did not protect the mice because they died at the same rate as controls. Such reference cannot be said to teach inducing a "protective" immune response.

Without a showing of a suggestion of these features in the references, and for the reasons given before, the rejection should be withdrawn.

Claim 55 was objected to as being an improper dependant claim for not further limiting the subject matter of claim 1. Claim 55 has been amended making this objection moot. Furthermore, contrary to the examiner's comments, the polypeptide in a plant extract is purified as can be seen in Examples 3 and 4 where secreted polypeptide (a purified product) is recovered from the interstitial fluid of a plant. New claim 57 highlights this and also represents yet another difference as the references applied in the rejections above recover polypeptides from homogenized whole plant tissue (a non-purified product).

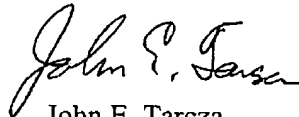
In view of the above amendments and comments, the claims are now in condition for allowance and applicants request a timely Notice of Allowance be issued in this

McCormick et al
U.S. Serial No. 09/522,900
Page 15 of 15

application. If needed, applicants petition for sufficient extension of time for consideration of this paper.

The commissioner hereby is authorized to charge payment of any fees, including extension of time fees, under 37 CFR § 1.17, which may become due in connection with the instant application or credit any overpayment to Deposit Account No.500933.

Respectfully submitted,



John E. Tarcza
Reg. No. 33,638

Date: April 24, 2006

Attachments: Petition for a Three-Month Extension of Time

John E. Tarcza
Intellectual Property Advisor
Large Scale Biology Corporation
3333 Vaca Valley Parkway, Suite 1000
Vacaville, CA 95688
301-371-7740 tel.
301-371-7745 Fax.
E-MAIL john.tarcza@lsbc.com